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# HOW I DO IT

# Introduction: Sentinel Lymphadenectomy for Patients With Clinical Stage I Melanoma

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Approximately 10–60% of patients diagnosed with cutaneous malignant melanoma have tumor involvement of the regional lymph nodes. Their overall rate of 5-year survival is only 30%–40%, reflecting the putative association between lymph node involvement and aggressive progression to distant metastases. Early identification and removal of tumor-involved lymph nodes can curtail the spread of melanoma, but prophylactic or elective lymphadenectomy (ELND) remains controversial. Retrospective reviews demonstrated a 15–25% improvement in survival [1–3]; prospective randomized trials initially showed no survival advantage but were noted to have inherent design flaws [4,5]. Recent results from the Intergroup Melanoma Trial demonstrated no overall survival advantage but identified subsets of patients for whom ELND appears to be beneficial (patients under 60 years old with primary melanomas 1–2 mm in thickness) [6].

In 1990, during a presentation to the Society of Surgical Oncology, we introduced intraoperative lymphatic mapping and sentinel lymphadenectomy (SLND) as a potential solution to the controversy surrounding ELND in patients with clinical stage I malignant melanoma. As first published in our 1992 report [7], SLND uses logical anatomic and physiologic principles to identify occult regional node metastases. Mastery of SLND eliminates routine ELND, thereby reducing overall health care costs and avoiding extensive resection of the lymph node basin in patients with tumor-free lymph nodes (who are unlikely to benefit from the procedure).

As described below, the technique of SLND has evolved in the hands of its originators at the John Wayne Cancer Institute (JWCI). It has also been successfully adopted by surgical oncologists at other centers. In this issue, Dr. John F. Thompson of the Sydney Melanoma Unit in Australia, Dr. Merrick Ross of M.D. Anderson Cancer Center in Houston, Dr. Douglas Reintgen of Moffitt Cancer Center in Tampa, and Dr. C.P. Karakousis of the Millard Fillmore Hospital/State University of New York in Buffalo, describe their technique and results for SLND in patients with primary cutaneous melanoma.

## PREOPERATIVE LYMPHOSCINTIGRAPHY

At JWCI we always obtain a dynamic preoperative lymphoscintigram before SLND. This is necessary not only to identify the lymphatic basin(s) draining a cutaneous melanoma but also to identify and mark the position of the sentinel node(s) and lymphatic channel(s). As the location of the primary moves from the distal extremity to the trunk and the head and neck, historical anatomic guidelines become increasingly inaccurate for identifying the primary lymphatic drainage basin(s) [8,9]. Moreover, approximately 25% of patients have more than one sentinel lymph node. Each of these sentinel nodes may receive drainage from one or more lymphatic channels, but no single channel drains into more than one sentinel node. By following the image of the lymphatic channel(s) into the identified sentinel lymph node(s), dynamic lymphoscintigraphy usually can distinguish multiple sentinel nodes from a solitary sentinel node with secondary drainage. In the 3–5% of patients with in-transit aberrant lymph nodes, lymphoscintigraphy can visualize nodes outside the lymphatic basin along the primary lymphatic channel. Multiple views are necessary to define the lymphatic anatomy and its location within the draining lymphatic basin.

Lymphoscintigraphy can be performed with a variety of agents that vary in particle size and composition. Particle size determines the time to optimum visualization: smaller, uniformly labeled particles are visualized faster than larger, nonuniform particles. As demonstrated in the following reports from Drs. Thompson, Reintgen and Ross, the timing of colloid injection varies considerably

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among institutions. At JWCI, we usually perform lymphoscintigraphy the day before or the morning of surgery, so that the mark placed on the skin by our nuclear medicine colleague (to identify the number and the location of lymphatic channels and sentinel node[s]) does not wear off. Also, when preoperative lymphoscintigraphy is performed no more than 24 hours before SLND, there is enough residual radioactivity to use the gamma probe as an adjunct for intraoperative localization of sentinel nodes (see below).

## INTRAOPERATIVE MAPPING: BLUE DYE AND PROBE

Intraoperative mapping can be carried out with a vital dye (usually patent blue or isosulfan blue), different nuclear agents of varying or uniform particle size, or a combination of dye and labeled agent. Although our initial approach to SLND used isosulfan dye alone, in 1993 we began using isosulfan blue mixed with radiolabeled human serum albumin; in 1994 we presented our results to the Society of Surgical Oncology [10]. We believe that a 2:1 combination of vital dye and radiolabeled pharmaceutical is additive in its ability to localize the sentinel node, and we now use both agents in every case.

An intradermal injection of 1–2 cc of the localizing agent is administered around the primary lesion. The exact volume of dye depends on the distance between the primary site and the nodal basin. If excisional biopsy has preceded definitive surgery, care must be taken not to inject the dye into the biopsy cavity. Accurate lymphatic mapping usually is not possible following a wide local excision using 2-cm margins, especially if local flaps or skin grafts have been used to close the defect [11]. When the dye is used, the interval between dye injection and surgical incision will vary depending upon the physiology of the patient and the distance between the site of injection and the draining lymphatic basin.

If a radiopharmaceutical is used, it is usually technetium-labeled sulfur colloid or human serum albumin. Intraoperative radiolymphoscintigraphy was originally introduced due to technical difficulties with the use of dye alone, especially in axillary drainage basins [7,10]. After the radiopharmaceutical is injected at the site of the primary tumor, a hand-held gamma probe is used to map the lymphatic channel(s), lymph node basin(s) and sentinel node(s) by monitoring the emitted counts in relationship to the background. No standardization has yet been established; guidelines for the ratio of counts between the sentinel node(s) and lymph node basin(s) have been proposed but vary widely among different authors [12–15].

A concerted effort must be made to identify the lymphatic channel since this is the key to detecting the true sentinel node(s). Meticulous dissection is employed to follow the channel both proximally (to rule out any proximal sentinel nodes) and distally into the sentinel node. Usually a short segment of the channel is excised with the lymph node. Surgical attention to detail and familiarity with the procedure have fostered success with SLND among surgeons at JWCI. We define surgical proficiency as 90% accuracy in identifying the sentinel node, which is usually reached after undertaking 30 cases. Most surgeons will achieve 98% accuracy after experience with 100 cases.

## EXAMINATION OF THE SENTINEL LYMPH NODE

Both Drs. Ross and Reintgen stress the importance of careful histopathologic evaluation of the sentinel node specimen. Even if localization and excision of sentinel nodes are successful, the results of SLND will not be accurate unless the pathologist undertakes a diligent search for nodal micrometastases. At JWCI, we bivalve the specimen and process its two faces immediately by frozen section analysis. Standard hematoxylin and eosin staining (H&E) is performed later on four sections, and all negative results are verified using immunohistochemical staining with HMB-45 and S-100 antibodies. Further surgical therapy is dictated by the results of histopathological analysis.

Serial sectioning and immunohistochemical analysis are more sensitive in detecting microscopic nodal metastases than is standard histopathologic preparation; we currently study 12 sections of the serially sectioned sentinel node. Results of cell culture of excised lymph node preparations have been used to upstage 21% of node-negative patients [16]. However, the time and expertise of this technique prohibit its general acceptance.

Submicroscopic molecular biologic techniques using reverse transcriptase polymerase chain reaction (RT-PCR) have been proposed as a method of identifying submicroscopic nodal metastases [17]. One study reported that 28% of nodes were upstaged with this modality [18]. Caution is necessary because capsular nevi, Schwann cells, and nerves are present in about 25% of sentinel nodes and may cause a false-positive tyrosinase signal [19]. However, Dr. Reintgen has previously reported interim follow-up data indicating that the disease-free interval is reduced considerably when nodes are identified as tumor-positive by standard histopathology and RT-PCR [20]. The metastatic cells are often found in the vicinity of the afferent lymphatic, in the subcapsular lymph node space.

## SUMMARY

Consistent results with SLND can only be obtained through the combined efforts of the nuclear medicine physician, the surgeon, and the pathologist. These individuals must have experience with the technical details of SLND and must understand and accept the multidisciplinary nature of this technique.

The reports in this issue of the *Journal of Surgical Oncology* prove that SLND is accurate and reproducible. Drs. Thompson and Karakousis both report a 93% rate of sentinel node identification, and Dr. Reintgen reports a rate of 96%. At JWCI, our overall rate of sentinel node identification has now reached 98%. The ultimate results of SLND as a therapeutic procedure in patients with clinical stage I cutaneous melanoma await completion of our international phase III multicenter trial (''A Clinical Study of Wide Excision Alone Versus Wide Excision with Intraoperative Lymphatic Mapping and Selective Lymph Node Dissection in the Treatment of Patients with Cutaneous Invasive Melanoma''; D.L. Morton, Principal Investigator), which is now in its third year of accrual. At the present time, we believe that lymphatic mapping and selective (sentinel) lymph node dissection is an investigational procedure whose therapeutic utility is unproven. Until clinical trials are completed and there is technique standardization among various centers, this procedure should not be used as routine therapy in a community hospital outside the setting of a clinical trial. Although intraoperative lymphatic mapping and SLND may provide prognostic information, if its therapeutic utility is not demonstrated by current multicenter clinical trials, it is likely to be replaced by molecular RT-PCR techniques that directly measure tumor burden in the blood [21].

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